Supplemental Materials

For

Parallel Synthesis and Antimalarial Screening of a 4-Aminoquinoline Library

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Compound	Yield	Purity		Compound	Yield	Purity
1{1,2}	10.2%	100.0%		1{1,13}	25.4%	88%
1{2,2}	23.9%	30.6%		1{2,13}	6.4%	71%
1{3,2}	29.8%	95.2%		1{3,13}	12.6%	100%
1{4,2}	24.7%	100.0%		1{4,13}	34.3%	100%
1{5,2}	19.5%	87.8%		1{5,13}	11.5%	100%
1{6,2}	4.8%	80.2%		1{6,13}	8.2%	77%
1{7,2}	21.7%	100.0%		1{7,13}	23.9%	98%
1{8,2}	40.7%	100.0%		1{8,13}	31.7%	99%
1{9,2}	11.6%	80.5%		1{9,13}	9.3%	95%
1{10,2}	27.1%	95.0%		1{10,13}	20.6%	100%
1{11,2}	15.1%	87.8%		1{11,13}	9.7%	87%
1{12,2}	26.4%	85.8%		1{12,13}	19.2%	90%
1{13,2}	56.1%	90.1%		1{13,13}	43.6%	100%
1{14,2}	23.8%	97.9%		1{14,13}	15.3%	100%
1{15,2}	79.1%	100.0%		1{15,13}	75.0%	88%
1{16,2}	53.3%	100.0%		1{16,13}	38.9%	98%
1{17,2}	11.1%	84.4%		1{17,13}	5.0%	85%
1{18,2}	12.4%	97.3%		1{18,13}	12.6%	97%
1{19,2}	2.7%	72.2%		1{19,13}	8.4%	86%
1{20,2}	66.6%	90.8%		1{20,13}	15.6%	100%
1{21,2}	39.8%	99.2%		1{21,13}	52.4%	100%
1{22,2}	29.2%	99.0%		1{22,13}	40.4%	100%
1{23,2}	47.6%	100.0%		1{23,13}	74.4%	84%
1{24,2}	83.4%	90.3%		1{24,13}	40.1%	100%

Table S1. Final yields and purities of library **1**. Yields were calculated based on the molar amount of the limiting reagent and the mass of final purified product obtained. Purity was assessed by analytical HPLC analysis monitored at 220 nm on a reversed-phase C18 column (Column Engineering, ReliaSil C18 BDX, 5 μM).

		Q-scores			
Compound	IC50 (nM)	30nM @ 72Hr	200nM @ 72Hr	30nM @ 96Hr	200nM @ 96Hr
CQ	23.5	0	0	0	0
4-amino-7-chloroquinoline		-12.88	-15.79	-24.60	-40.52
1{*1,2*}		-1.81	0.00	-0.95	-0.43
1{*3,2*}		na	-0.47	na	-0.87
1{*4,2*}		-5.52	0.05	-19.98	-0.43
1{*5,2*}		-4.70	0.34	-9.98	-0.35
1{*6,2*}		-12.30	0.16	-23.83	-0.26
1{*7,2*}		-8.75	0.66	-23.25	-0.30
1{*8,2*}		-7.97	0.23	-22.20	-0.70
1{*9,2*}		-7.45	0.16	-24.50	-0.57
1{*10,2*}		-7.94	0.23	-23.20	-0.48
1{*11,2*}		-12.43	-0.06	-25.00	-0.43
1{*12,2*}		-4.03	0.00	-20.40	-0.30
1{*13,2*}	19.5	-1.32	0.00	-1.08	-0.35
1{*14,2*}		-6.65	0.11	-20.58	-0.17
1{*15,2*}		-12.52	-7.69	-23.43	-27.61
1{*16,2*}	11.0	0.32	0.23	0.25	-0.13
1{*17,2*}		-13.08	-3.89	-24.50	-12.13
1{*18,2*}		-9.77	-2.11	-24.85	-2.26
1{*19,2*}		-10.04	0.23	-23.68	-0.48
1{*20,2*}		-10.34	-0.11	-22.23	-0.35
1{*21,2*}	19.5	-0.36	-0.11	-0.10	-0.57
1{*22,2*}	18.5	-0.09	-0.06	-0.10	-0.83
1{*23,2*}		-11.44	0.00	-23.43	-0.48
1{*24,2*}		-12.34	-2.34	-23.13	-3.83
1{*1,13*}		-10.06	0.23	-19.90	-0.35
1{*2,13*}		-11.88	0.16	-25.15	-0.30
1{*3,13*}		-6.60	-1.03	-21.53	-1.17
1{*4,13*}		-5.18	0.34	-18.68	-0.30
1{*5,13*}		-8.75	-1.77	-22.05	-6.61
1{*6,13*}		-8.95	-2.18	-23.68	-2.04
1{*7,13*}		-8.12	-3.48	-22.70	-13.17
1{*8,13*}		-8.86	-3.37	-26.23	-14.00
1{*9,13*}		-9.55	0.34	-22.35	-0.43
1{*10,13*}		-8.90	-3.48	-24.60	-12.35
1{*11,13*}		-12.34	-5.94	-25.35	-29.65

1{*12,13*}		-10.73	-2.97	-21.85	-9.35
1{*13,13*}		-7.61	-3.03	-21.23	-10.91
1{*14,13*}		-11.51	-3.82	-24.65	-15.35
1{*15,13*}		-13.26	-1.66	-24.98	-2.61
1{*16,13*}		-12.30	-0.26	-25.33	-2.00
1{*17,13*}		-15.74	-14.66	-23.33	-40.52
1{*18,13*}		-10.78	-4.27	-25.58	-16.35
1{*19,13*}		-12.01	-3.08	-25.10	-8.35
1{*20,13*}		-10.64	-2.81	-24.98	-2.70
1{*21,13*}		-11.47	-3.42	-23.35	-5.61
1{*22,13*}		-12.52	-4.63	-23.65	-15.78
1{*23,13*}	17.0	0.14	0.11	0.15	-0.43
1{*24,13*}		-12.94	-13.34	-22.70	-43.22

Table S2. Full activity data for library **1**. Q-scores are a normalized activity measure calculated as (Parasite survival in presence of CQ – Parasite survival in presence of compound) / (Parasite survival in presence of CQ). IC_{50}s were estimated from dose response curves from 1 nm to 200 nm drug concentrations.

Compound 1{1,2}
^{1}H NMR (CD_3OD): δ 8.49 (d, J = 8.7, 1H), δ 8.46 (d, J = 6.8, 1H), δ 7.90 (d, J = 1.9, 1H), δ 7.72 (dd, J = 8.7, J = 1.9, 1H), δ 6.98 (d, J = 6.8, 1H), δ 3.74 (t, J = 6.8, 2H), δ 3.25 – 3.35 (m, overlap w/solvent), δ 3.14 (m, 2H), δ 2.22 (m, 2H), δ 1.77 (m, 2H), δ 1.35 (t, J = 6.8, 3H), δ 1.03 (t, J = 6.8, 3H). MS: ESI+ 306.0 [M + 1] Calc. Mass: 305.2.

Compound 1{3,2}
^{1}H NMR (CD_3OD): δ 8.57 (d, J = 8.8, 1H), δ 8.47 (d, J = 6.8, 1H), δ 7.91 (d, J = 1.9, 1H), δ 7.72 (dd, J = 8.8, J = 1.9, 1H), δ 7.02 (d, J = 6.8, 1H), δ 3.75 (m, 2H), δ 3.25 – 3.35 (m, overlap w/solvent), δ 3.16 (m, 2H), δ 3.04 (d, J = 5.8, 2H), δ 2.28 (m, 2H), δ 2.15 (m, 1H), δ 1.75 (m, 2H), δ 1.06 (d, J = 5.8, 6H), δ 1.00 (t, J = 6.8, 3H). MS: ESI+ 333.9 [M + 1] Calc. Mass: 333.2.

Compound 1{4,2}
^{1}H NMR (CD_3OD): δ 8.52 (d, J = 8.8 Hz, 1H), δ 8.46 (d, J = 5.9 Hz, 1H), δ 7.90 (d, J = 1.9, 1H), δ 7.00 (dd, J = 5.9, J = 1.9, 1H), δ 3.75 (t, J = 4.88, 2H), δ 3.42 (m, 2H), δ 3.42 (m, 2H), δ 3.20 – 3.35 (m, overlap w/solvent), δ 3.13 (d, J = 6.8, 2H), δ 2.26 (m, 2H), δ 1.80 (m, 2H), δ 1.16 (m, 1H), δ 1.03 (t, J = 6.8, 3H), δ 0.75 (m, 2H), δ 0.46 (m, 2H). MS: ESI+ 332.0 [M + 1] Calc. Mass: 331.2.

Compound 1{7,2}
^{1}H NMR (CD_3OD): δ 8.52 (d, J = 9.7, 1H), δ 8.46 (d, J = 6.8, 1H), δ 7.90 (d, J = 1.9, 1H), δ 7.72 (dd, J = 8.8, J = 1.9, 1H), δ 7.00 (d, J = 6.8, 1H), δ 3.74 (t, J = 6.8, 2H), δ 3.25 – 3.35 (m, overlap w/solvent), δ 3.18 (m, 4H), δ 2.25 (m, 2H), δ 1.77 (m, 2H), δ 1.64 (m, 3H), δ 1.02 (t, J = 6.8, 3H), δ 0.96 (d, J = 6.8, 6H). MS: ESI+ 348.1 [M + 1] Calc. Mass 347.2.

Compound 1{8,2}
^{1}H NMR (CD_3OD): δ 8.57 (d, J = 9.7, 1H), δ 8.47 (d, J = 5.8, 1H), δ 7.91 (d, J = 1.9, 1H), δ 7.72 (dd, J = 8.8, J = 1.9, 1H), δ 7.02 (d, J = 6.8, 1H), δ 3.76 (m, 2H), δ 3.25 – 3.40 (m, overlap w/solvent), δ 3.21 (m, 4H), δ 2.26 (m, 2H), δ 1.79 (m, 2H), δ 1.65 (m, 2H), δ 0.93 – 1.04 (m, 12H). MS: ESI+ 361.9 [M + 1] Calc. Mass 361.2.

Compound 1{14,2}
^{1}H NMR (CD_3OD): δ 8.45 (d, J = 6.8, 1H), δ 8.40 (d, J = 8.8, 1H), δ 7.92 (d, J = 1.9, 1H), δ 7.74 (dd, J = 8.8, J = 1.9, 1H), δ 7.45 (m, 4H), δ 6.91 (d, J = 6.8, 1H), δ 4.43 (d, J = 12.6, 1H), δ 4.32 (d, J = 12.6, 1H), δ 3.69 (t, J = 4.8, 2H), δ 3.25 – 3.35 (m, overlap w/solvent), δ 3.16 (t, J = 8.8, 2H), δ 2.27 (m, 1H), δ 2.20 (m, 1H), δ 1.85 (m, 2H), δ 1.01 (t, J = 7.8, 3H). MS: ESI+ 446.0 [M + 1] Calc. Mass 445.1.

Compound 1{22,2}
^{1}H NMR (CD_3OD): δ 8.47 (d, J = 8.8, 1H), δ 8.45 (d, J = 6.8, 1H), δ 7.91 (d, J = 1.9, 1H), δ 7.72 (m, 2H), δ 7.48 (m, 1H), δ 7.27 (d, J = 4.8, 1H), δ 6.95 (d, J = 6.8, 1H), δ 4.44 (s, 2H), δ 3.71 (t, J = 5.7, 2H), δ 3.25 – 3.35 (m, overlap w/solvent), δ 3.11 (m, 2H), δ 2.27 (m, 2H), δ 1.83 (m, 2H), δ 0.99 (t, J = 6.8, 3H). MS: ESI+ 373.8 [M + 1] Calc. Mass 373.1

Compound 1{23,2}
^{1}H NMR (CD_3OD): δ 9.07 (s, 1H), δ 8.58 (d, J = 8.8, 1H), δ 8.46 (m, 1H), δ 8.01 (m, 1H), δ 7.91 (d, J = 1.9, 1H), δ 7.70 (dd, J = 8.8, J = 1.9, 1H), δ 7.04 (d, J = 8.8, 1H), δ 4.67 (s, 2H), δ 3.78 (m, 2H), δ 3.44 (m, 2H), δ 3.25 – 3.35 (m, overlap w/solvent), δ 3.21 (m, 2H), δ 2.38 (m, 2H), δ 1.89 (m, 2H), δ 1.03 (t, J = 5.8, 3H). MS: ESI+ 358.0 [M + 1] Calc. Mass 357.2

Compound 1{3,13}
^{1}H NMR (CD_3OD): δ 8.45 (m, 2H), δ 7.91 (d, J = 1.9, 1H), δ 7.73 (dd, J = 8.8, J = 1.9, 1H), δ 7.53 (m, 2H), δ 7.40 (m, 3H), δ 6.96 (d, J = 6.8, 1H), δ 4.43 (sb, 2H), δ 3.72 (t, J = 6.8, 2H), δ 3.25 – 3.25 (m, overlap w/solvent), δ 2.33 (m, 2H), δ 2.10 (m, 1H), δ 1.04 (d, J = 6.8, 3H), δ 0.96 (d, J = 6.8, 3H). MS: ESI+ 381.9 [M + 1] Calc. Mass 381.2

Compound 1{4,13}
^{1}H NMR (CD_3OD): δ 8.44 (m, 2H), δ 7.91 (d, J = 1.95, 1H), δ 7.71 (dd, J = 8.8, J = 1.9, 1H), δ 7.54 (m, 2H), δ 7.35 (m, 3H), δ 6.94 (d, J = 6.8, 1H), δ 4.54 (d, J = 12.7, 1H), δ 4.40 (d, J = 12.7, 1H), δ 3.71 (t, J = 6.8, 2H), δ 3.25 – 3.35 (m, overlap w/solvent), δ 3.13 (m, 2H), δ 2.28 (m, 2H), δ 1.23 (m, 1H), δ 0.76 (d, J = 7.8, 2H), δ 0.43 (m, 2H). MS: ESI+ 380.0 [M + 1] Calc. Mass 379.2

Compound 1{5,13}
^{1}H NMR (CD_3OD): δ 8.48 (d, J = 8.8, 1H), δ 8.47 (d, J = 6.8, 1H), δ 7.91 (d, J = 1.9, 1H), δ7.74 (dd, J = 8.8, J = 1.9, 1H), δ 7.58 (m, 2H), δ 7.44 (m, 3H), δ 6.99 (d, J = 6.8, 1H), δ 4.50 (d, J = 12.6, 1H), δ 4.39 (d, J = 12.6, 1H), δ 3.74 (t, J = 6.8, 2H), δ 3.43 (t, J = 7.8, 2H), δ 3.15 – 3.30 (m, overlap w/solvent), δ 2.40 (m, 2H), δ 0.98 (s, 9H). MS: ESI+ 396.0 [M + 1] Calc. Mass 395.2

Compound 1{7,13}
^{1}H NMR (CD_3OD): δ 8.44 (d, J = 6.8, 1H), δ 8.43 (d, J = 8.8, 1H), δ 7.91 (d, J = 1.9, 1H), δ 7.73 (dd, J = 8.8, J = 1.9, 1H), δ 7.53 (m, 2H), δ 7.35 (m, 3H), δ 6.93 (d, J = 6.8, 1H), δ 4.41 (d, J = 3.9, 2H), δ 3.70 (t, J = 6.8, 2H), δ 3.25 – 3.35 (m, overlap w/solvent), δ 3.19 (m, 2H), δ 2.27 (m, 2H), δ 1.67 (m, 3H), δ 0.92 (d, J = 4.8, 6H). MS: ESI+ 396.1 [M + 1] Calc. Mass 395.2

Compound 1{8,13}
^{1}H NMR (CD_3OD): δ 8.45 (m, 2H), δ 7.91 (d, J = 1.9, 1H), δ 7.73 (dd, J = 8.8, J = 1.9, 1H), δ 7.54 (m, 2H), δ 7.37 (m, 3H), δ 6.94 (d, J = 6.8, 2H), δ 4.41 (sb, 2H), δ 3.71 (t, J = 6.8, 2H), δ 3.25 – 2.35 (m, overlap w/solvent), δ 3.21 (m, 2H), δ 2.26 (m, 2H), δ 1.70 (m, 2H), δ 0.92 (s, 9H). MS: ESI+ 409.9 [M + 1] Calc. Mass 409.2

Compound 1{9,13}
^{1}H NMR (CD_3OD): δ 8.45 (d, J = 6.8, 1H), δ 8.41 (d, J = 8.8, 1H), δ 7.91 (d, J = 1.9, 1H), δ 7.73 (dd, J = 8.8, J = 1.9, 1H), δ 7.53 (m, 2H), δ 7.37 (m, 3H), δ 6.94 (d, J = 6.8, 1H), δ 4.42 (d, J = 3.9, 2H), δ 3.71 (t, J = 5.8, 2H), δ 3.20 – 3.35 (m, overlap w/solvent), δ 2.56 (t, J = 6.8, 2H), δ 2.26 (m, 4H), δ 2.12 (m, 2H), δ 2.07 (s, 3H). MS: ESI+ 413.7 [M + 1] Calc. Mass 413.2

Compound 1{13,13}
^{1}H NMR (CD_3OD): δ 8.43 (d, J = 6.8, 1H), δ 8.35 (d, J = 8.8, 1H), δ 7.91 (d, J = 1.9, 1H), δ 7.71 (dd, J = 8.8, J = 1.9, 1H), δ 7.52 (m, 4H), δ 7.37 (m, 6H), δ 6.87 (d, J = 6.8, 1H), δ 4.42 (sb, 4H), δ 3.64 (t, J = 6.8, 2H), δ 3.25 – 3.35 (m, overlap w/solvent), δ 3.26 (m, 2H), δ 2.27 (m, 2H). MS: ESI+ 415.6 [M + 1] Calc. Mass 415.2

Compound 1{14,13}
^{1}H NMR (CD_3OD): δ 8.45 (d, J = 6.8, 1H), δ 8.30 (d, J = 9.7, 1H), δ 7.91 (d, J = 1.9, 1H), δ 7.74 (dd, J = 8.8, J = 1.9, 1H), δ 7.53 (m, 2H), δ 7.48 (d, J = 8.8, 2H), δ 7.41 (d, J = 8.8, 2H), δ 7.39 (m, 3H), δ 6.86 (d, J = 6.8, 1H), δ 4.44 (sb, 2H), δ 4.30 (d, J = 16.6, 2H), δ 3.64 (t, J = 6.8, 2H), δ 3.25 – 3.35 (m, overlap w/solvent), δ 3.21 (m, 2H), δ 2.26 (m, 2H). MS: ESI+ 494.0 [M + 1] Calc. Mass 493.1

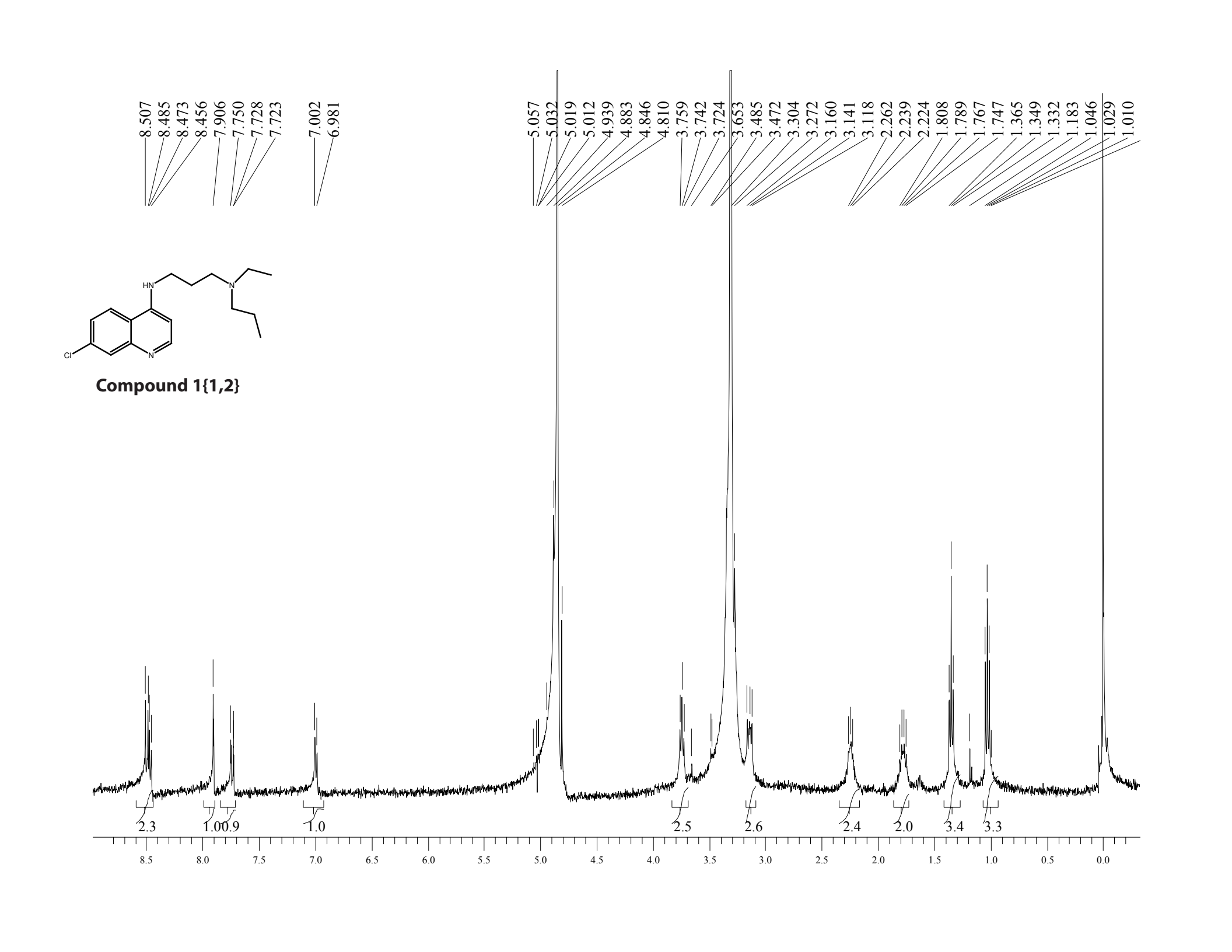
Compound 1{18,13}
^{1}H NMR (CD_3OD): δ 8.44 (d, J = 6.8, 1H), δ 8.40 (d, J = 8.8, 1H), δ 7.91 (d, J = 1.9, 1H), δ 7.77 (dd, J = 8.8, J = 1.9, 1H), δ 7.17 – 7.40 (m, 10H), δ 6.90 (d, J = 6.8, 1H), δ 4.40 (d, J = 4.8, 2H), δ 3.66 (t, J = 6.8, 2H), δ 3.25 – 3.35 (m, overlap w/solvent), δ 3.15 (m, 1H), δ 2.84 (m, 1H), δ 2.73 (m, 1H), δ 2.10 (m, 3H), δ 1.28 (d, J = 6.8, 3H). MS: ESI+ 457.5 [M + 1] Calc. Mass 457.2

Compound 1{20,13}
^{1}H NMR (CD_3OD): δ 8.87 (d, J = 4.8, 2H), δ 8.44 (dd, J = 8.8, J = 6.8, 2H), δ 8.38 (d, J = 4.8, 2H), δ 7.91 (d, J = 1.9, 1H), δ 7.72 (dd, J = 8.8, J = 1.9, 1H), δ 7.55 (m, 2H), δ 7.29 (m, 3H), δ 6.93 (d, J = 6.8, 1H), δ 4.45 (m, 4H), δ 3.69 (t, J = 6.8, 2H), δ 3.25 – 3.35 (m, overlap w/solvent), δ 2.40 (m, 2H). MS: ESI+ 417.0 [M + 1] Calc. Mass 416.2

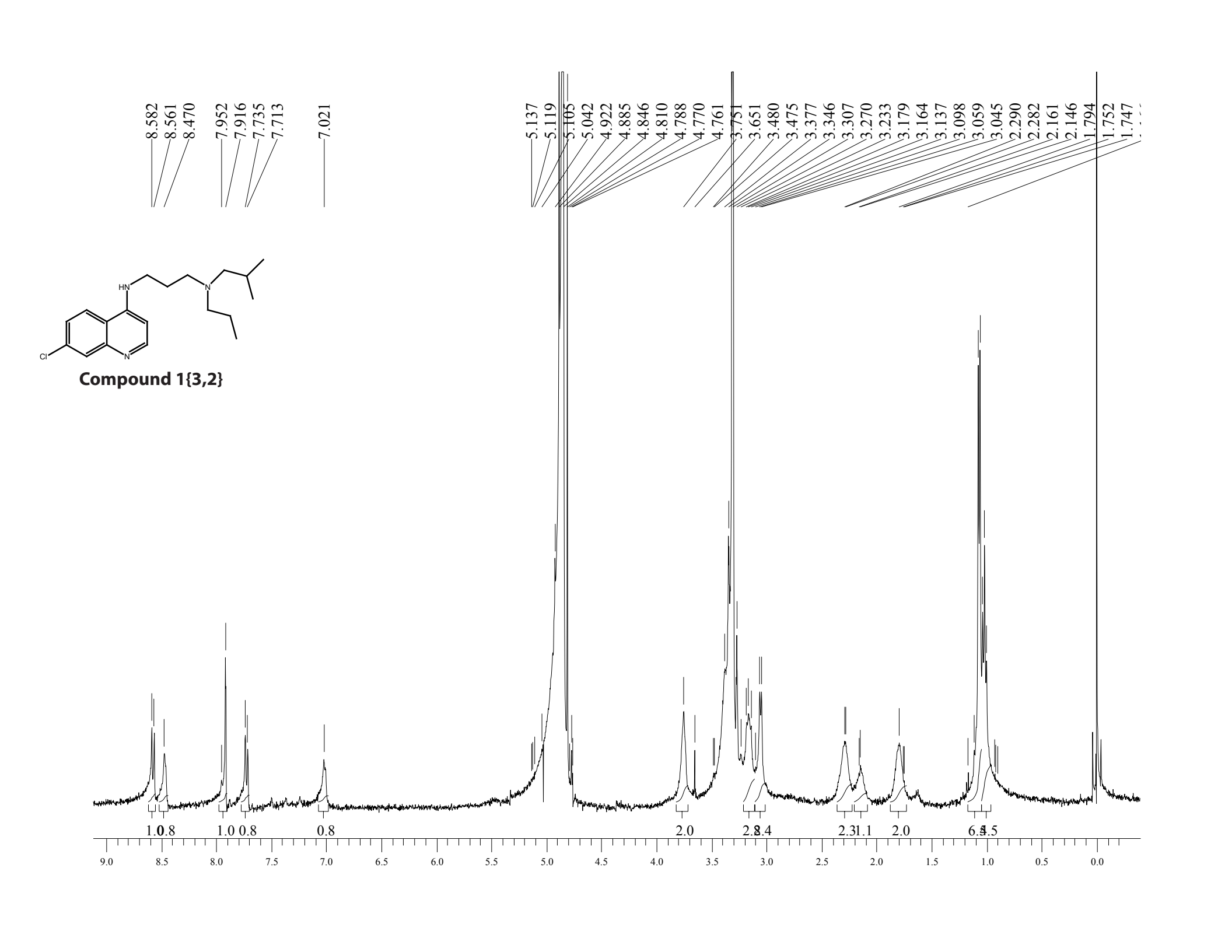
Compound 1{23,13}
^{1}H NMR (CD_3OD): δ 9.036 (s, 1H), δ 8.46 (d, J = 8.8, 1H), δ 8.43 (d, J = 6.8, 1H), δ 7.97 (s, 1H), δ 7.92 (d, J = 1.9), δ 7.70 (dd, J = 8.8, J = 1.9, 1H), δ 7.60 (m, 2H), δ 7.30 (m, 3H), δ 6.92 (d, J = 6.8, 1H), δ 4.69 (s, 2H), δ 4.49 (s, 2H), δ 3.69 (m, 2H), δ 3.34 (m, 2H), δ 2.34 (m, 2H). MS: ESI+ 405.6 [M + 1] Calc. Mass 405.2

Compound 1{24,13}

^{1}H NMR (CD_3OD): δ 8.45 (m, 2H), δ 7.93 (d, J = 1.9, 1H), δ 7.86 (d, J = 2.9, 1H), δ 7.72 (m, 2H), δ 7.59 (m, 2H), δ 7.39 (m, 3H), δ 6.94 (d, J = 6.8, 1H), δ 4.58 (m, 2H), δ 3.71 (t, J = 6.8, 2H), δ 3.44 (t, J = 6.8, 2H), δ 3.25 – 2.35 (m, overlap w/solvent), δ 2.38 (m, 2H).
MS: ESI+ 422.5 [M + 1] Calc. Mass 422.1



Compound 1{1,2}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N
Cl
N
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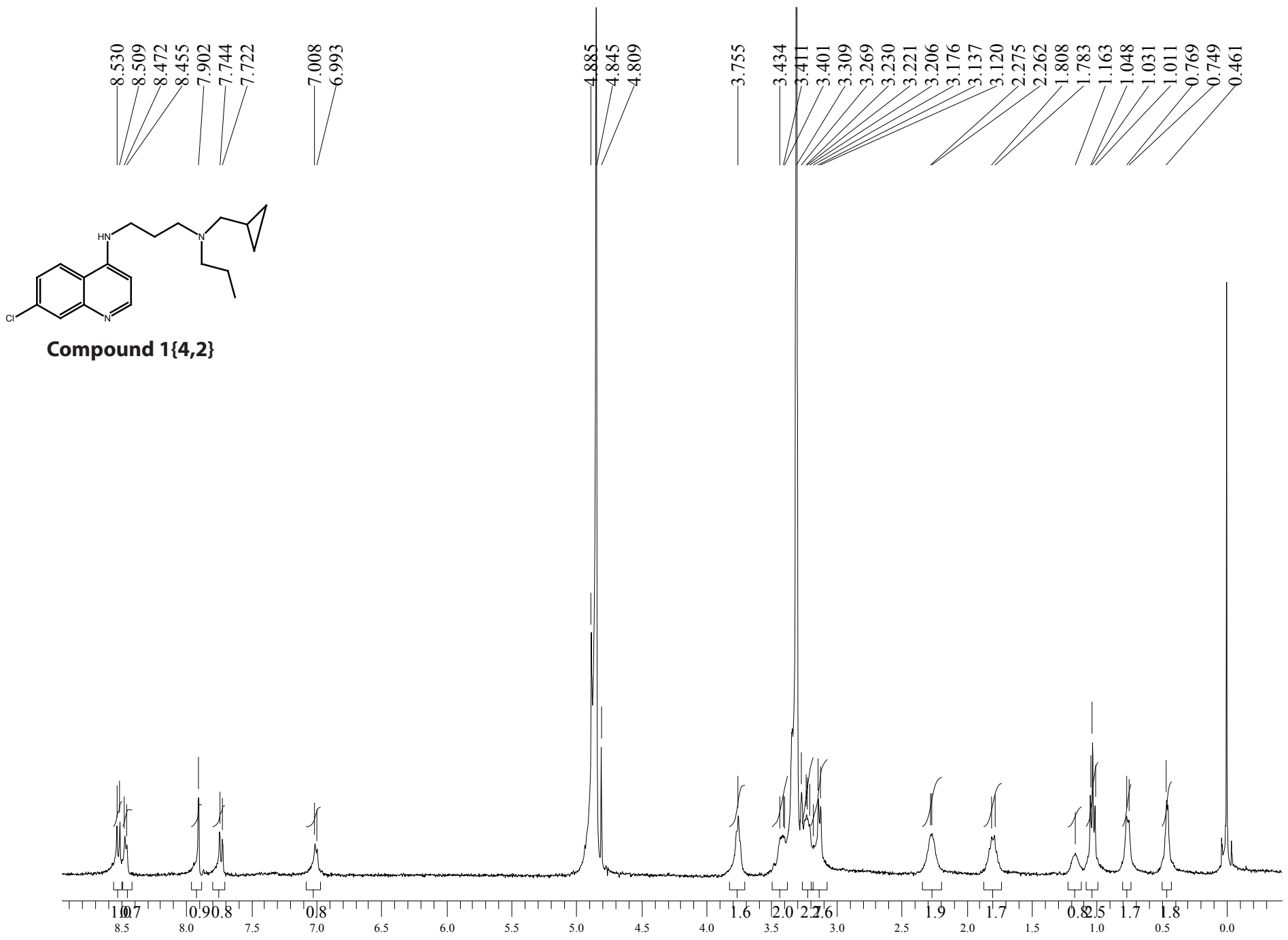
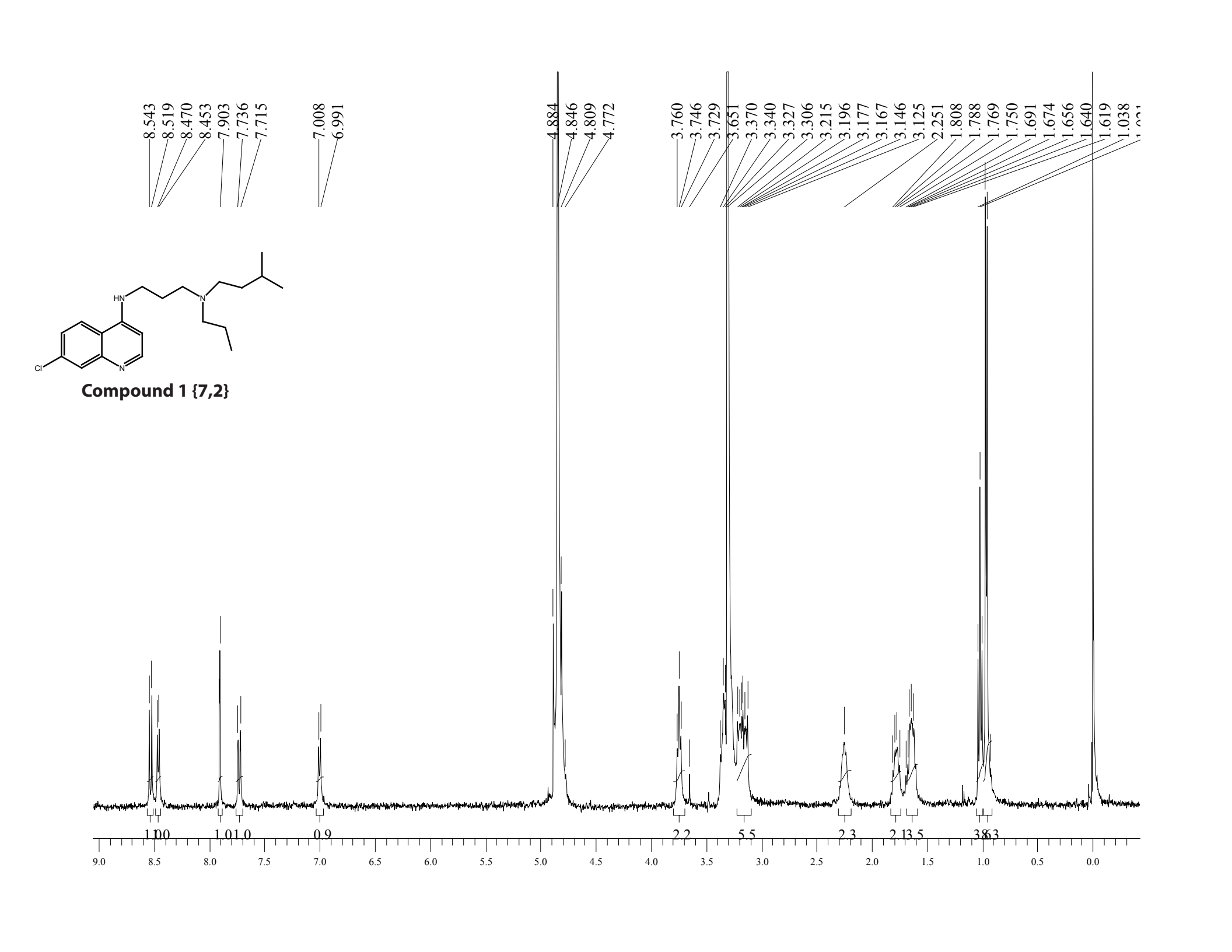
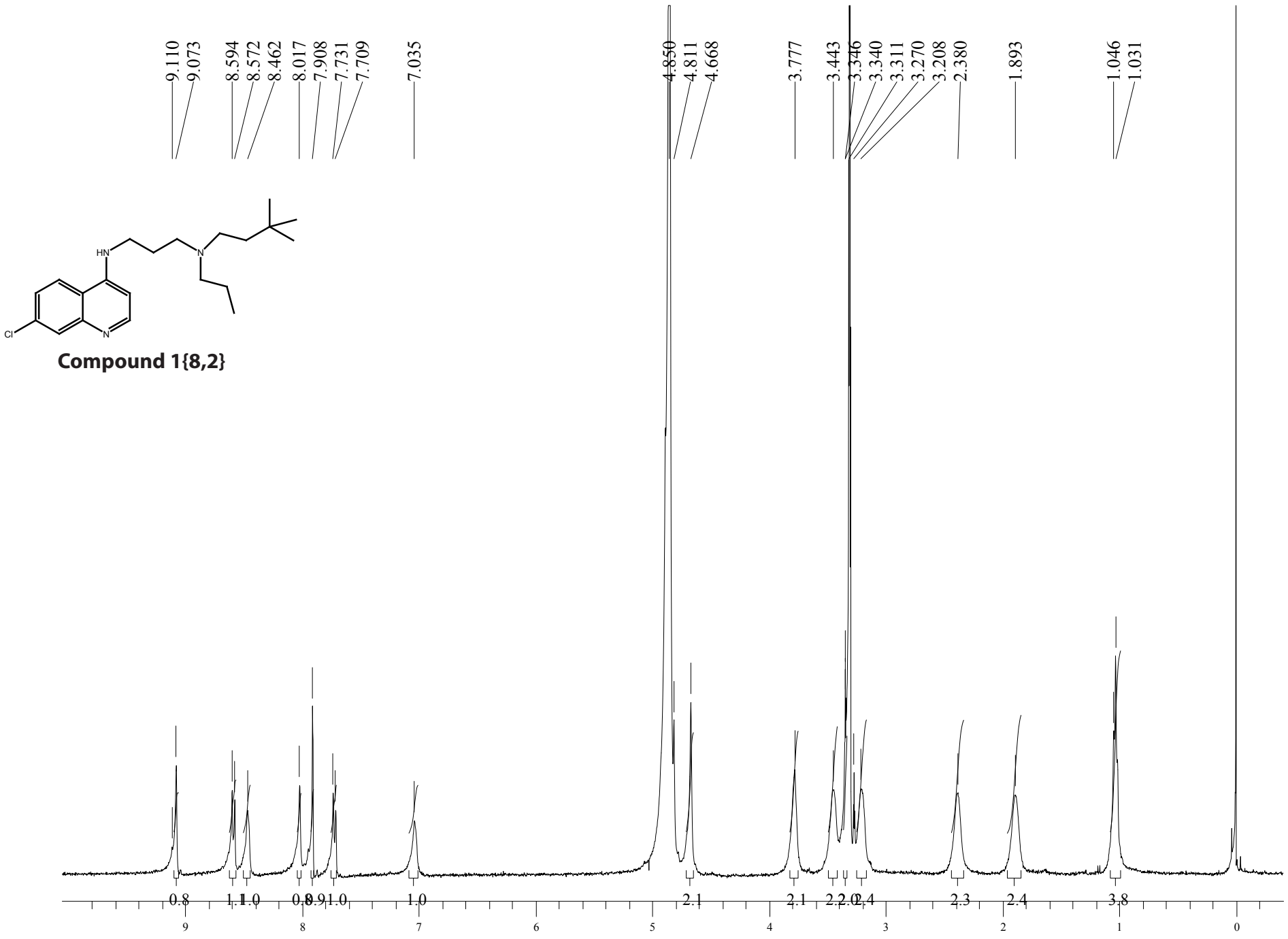


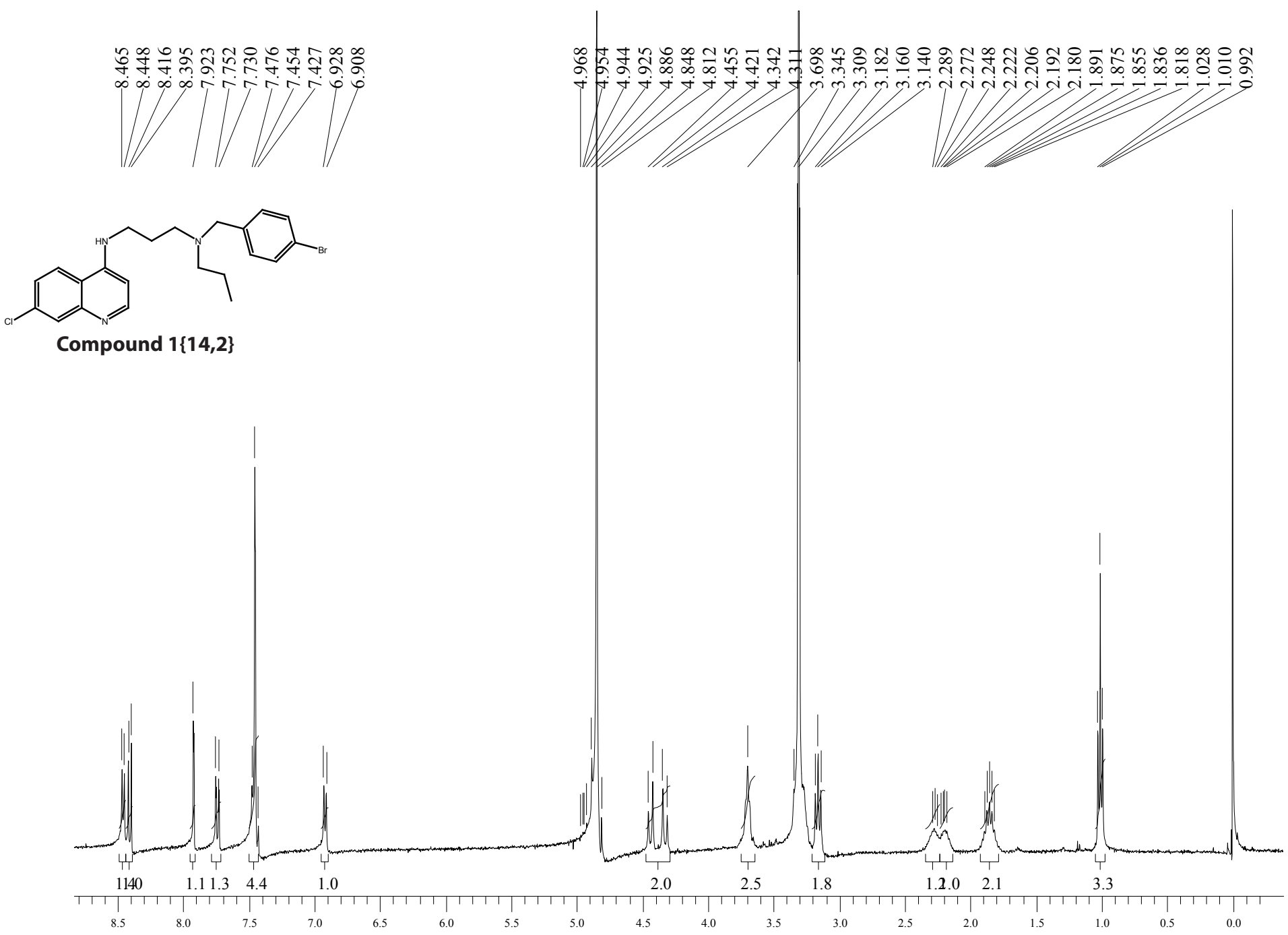
Compound 1{4,2}



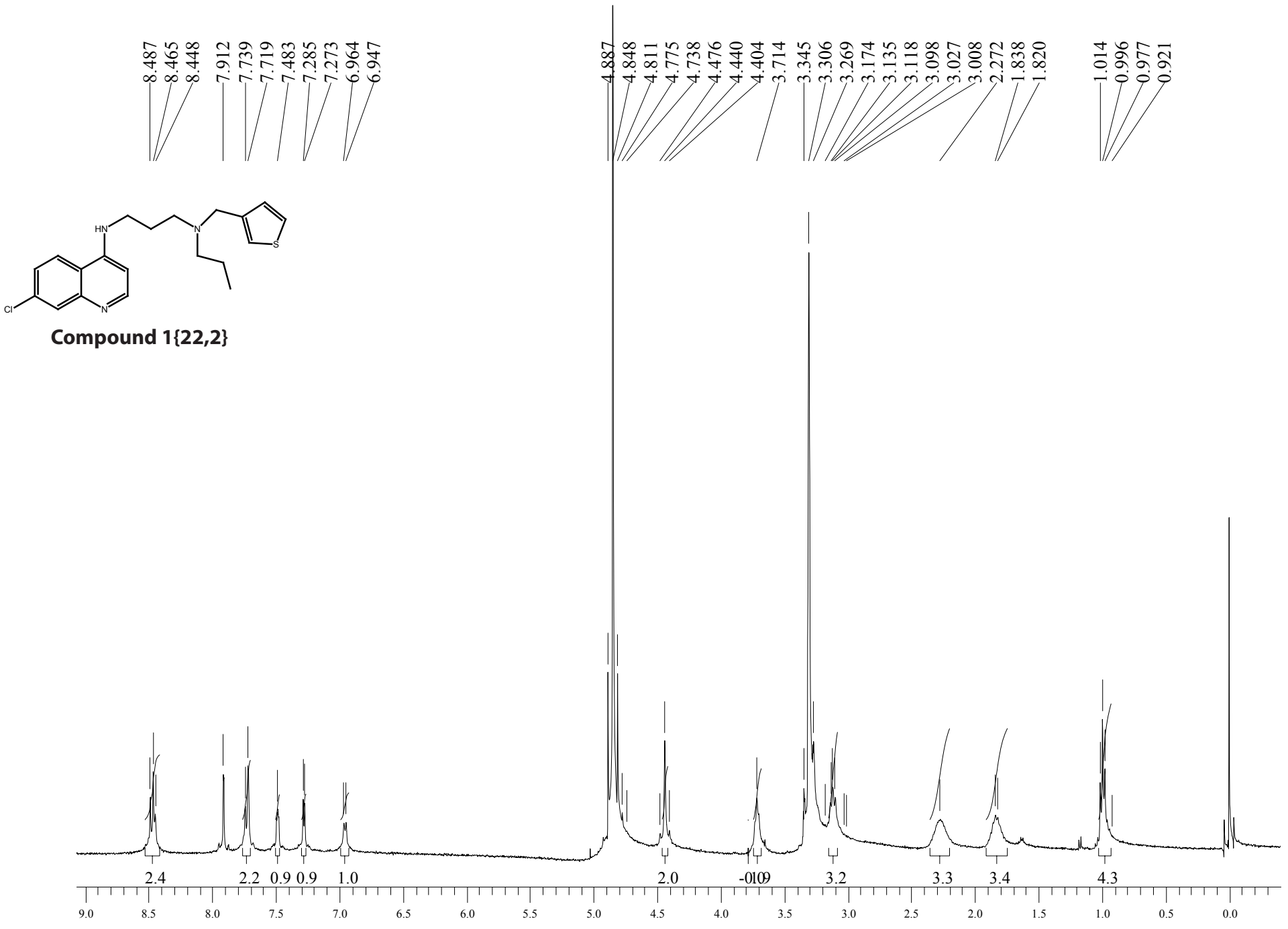
Compound 1 {7,2}



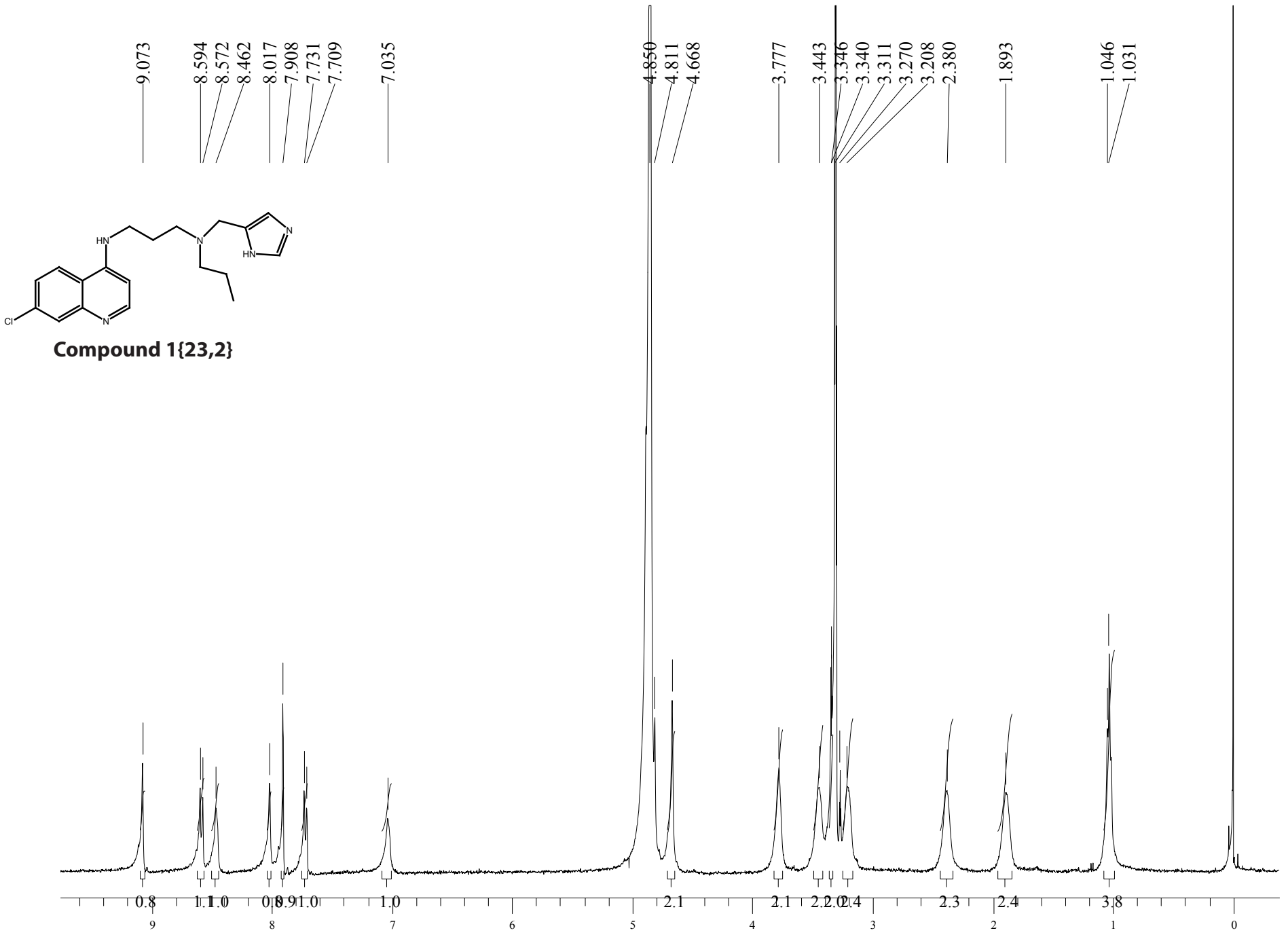
Compound 1{8,2}



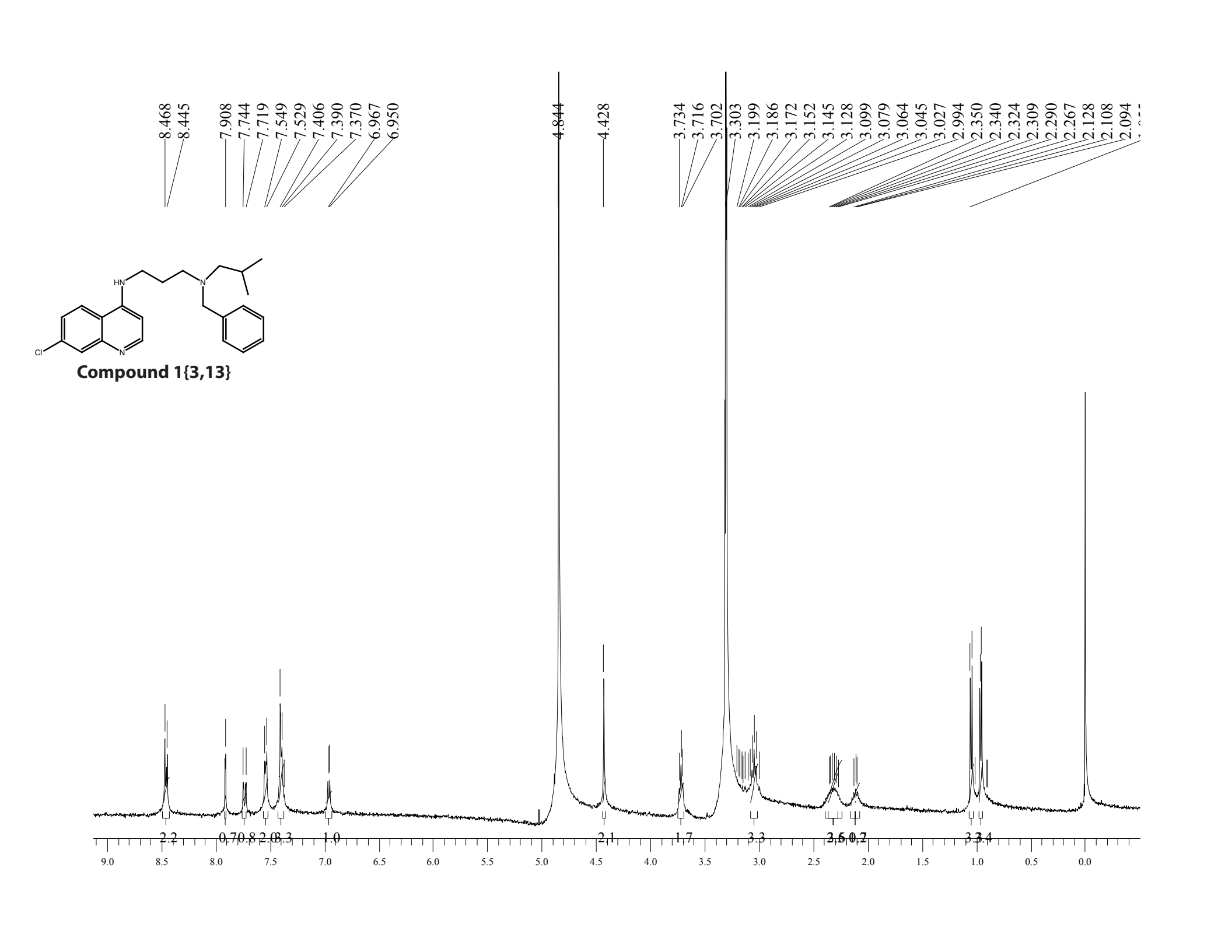
Compound 1{14,2}

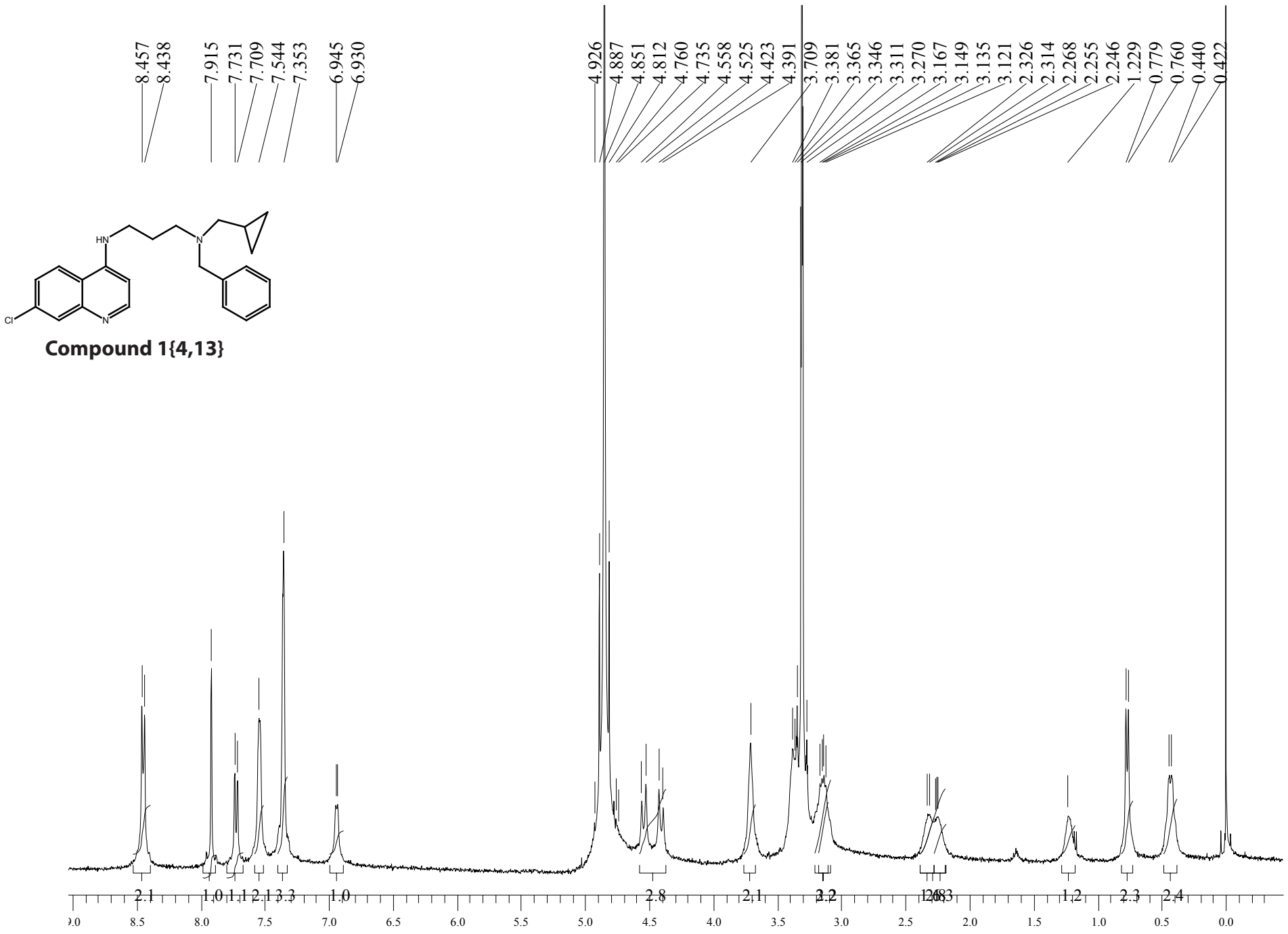


Compound 1{22,2}

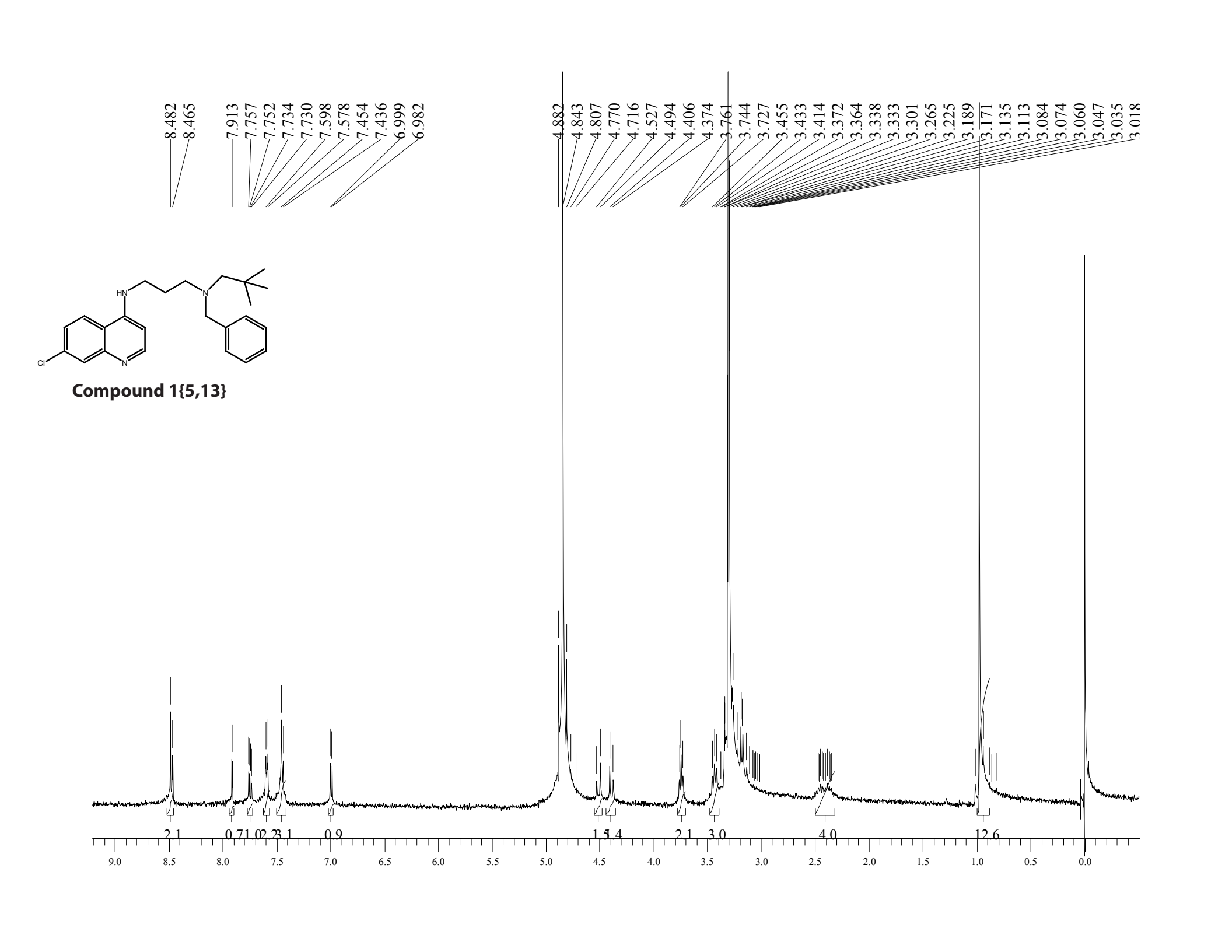


Compound 1{23,2}

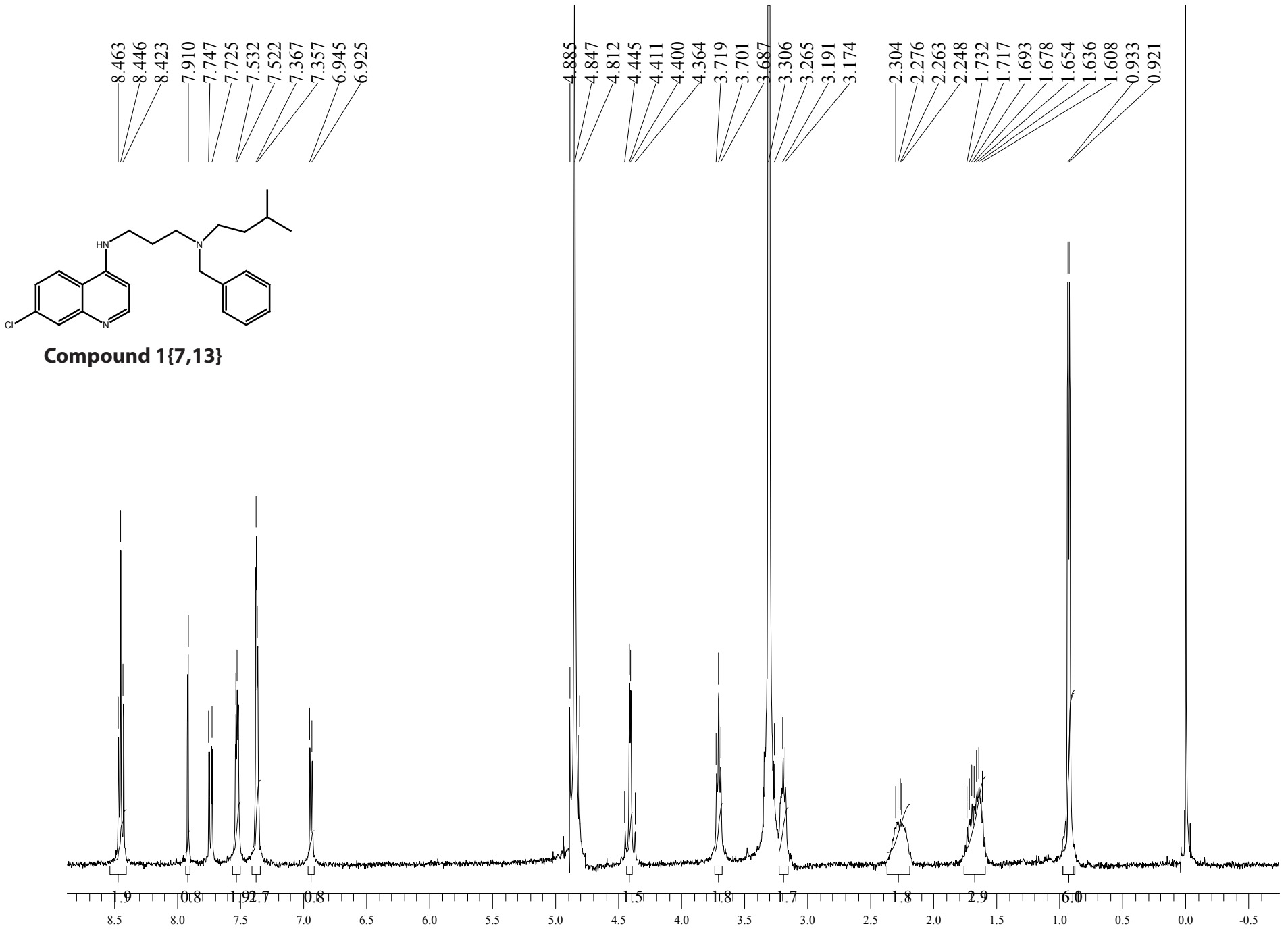

8.468
8.445
7.908
7.744
7.719
7.549
7.529
7.406
7.390
7.370
6.967
6.950
4.844
4.428
3.734
3.716
3.702
3.303
3.199
3.186
3.172
3.152
3.145
3.128
3.099
3.079
3.064
3.045
3.027
2.994
2.350
2.340
2.324
2.309
2.290
2.267
2.128
2.108
2.094
HN
N
Cl
N
Compound 1{3,13}
2.2
0.7
0.8
2.0
3.3
1.0
2.1
1.7
3.3
3.5
0.7
3.3
3.4
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0



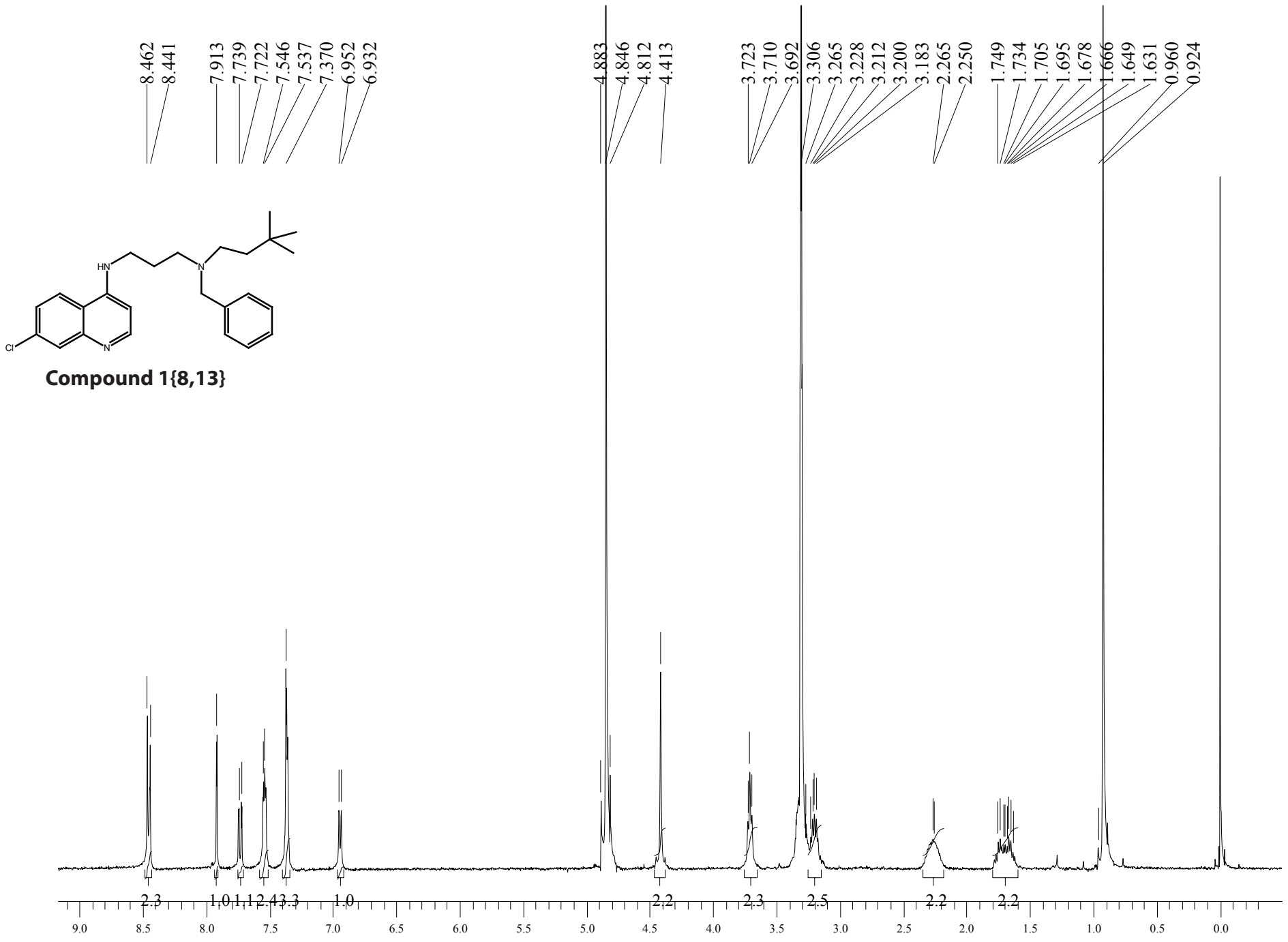
Compound 1{4,13}



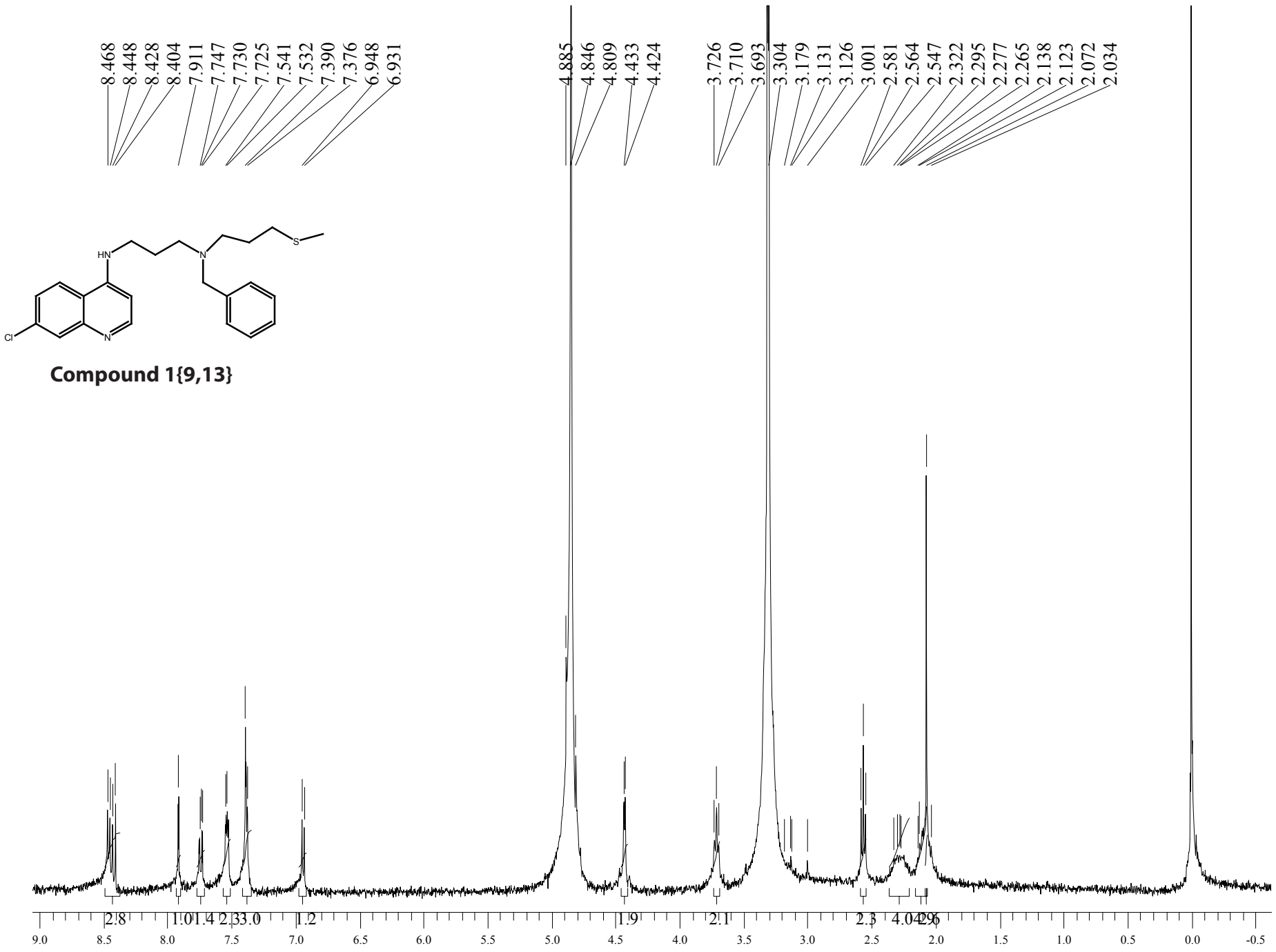
Compound 1{5,13}



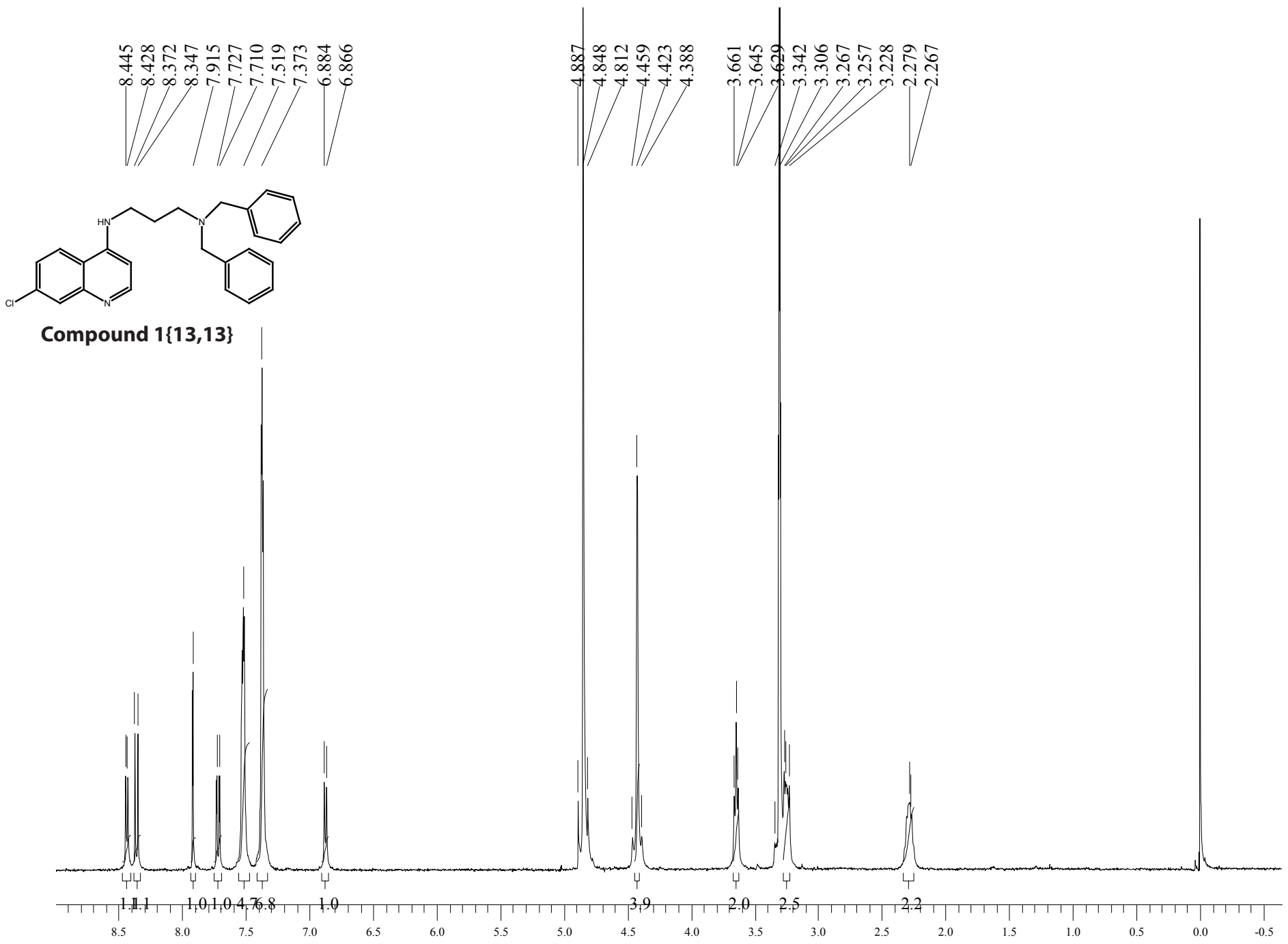
Compound 1{7,13}

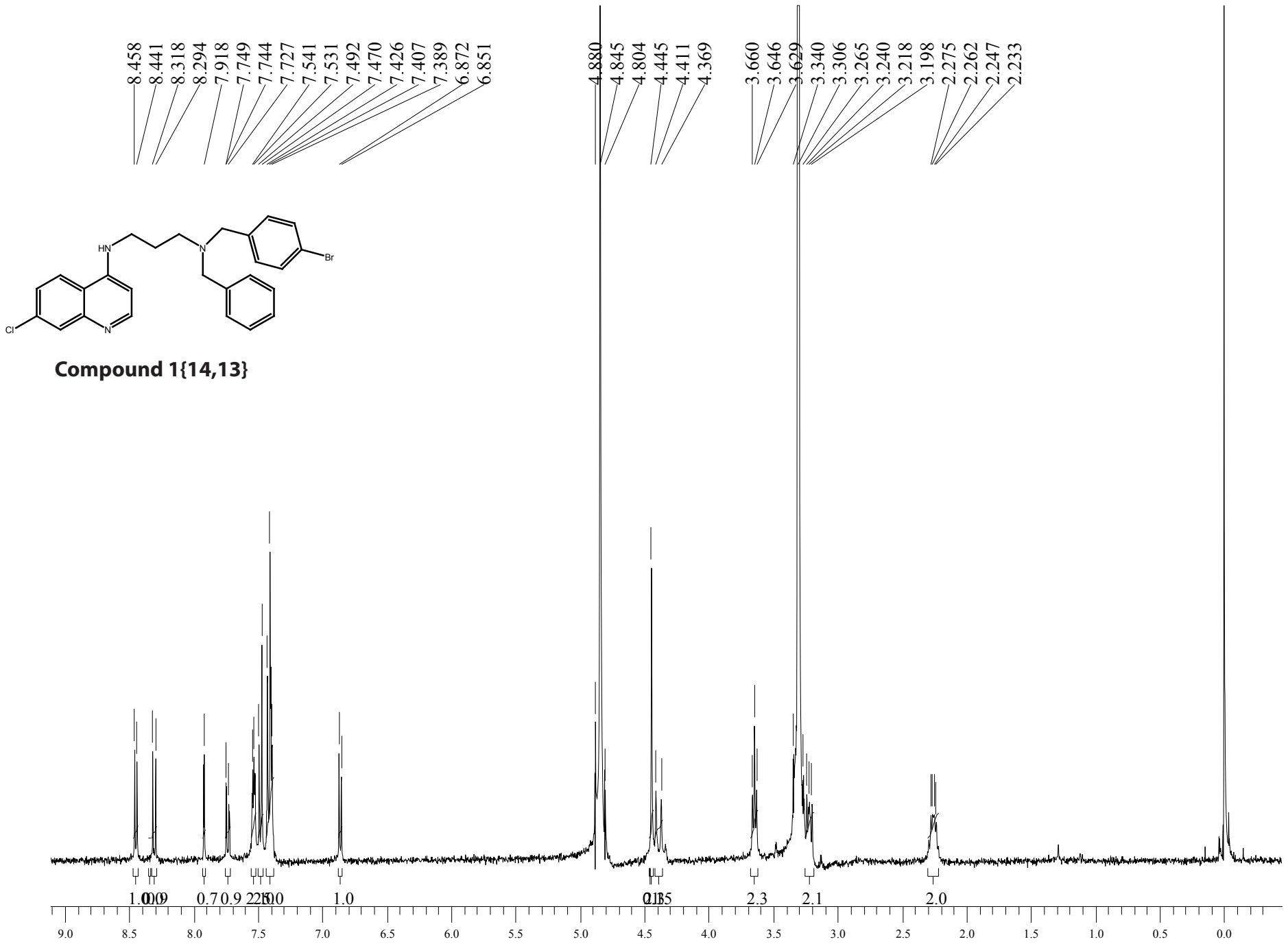


Compound 1{8,13}

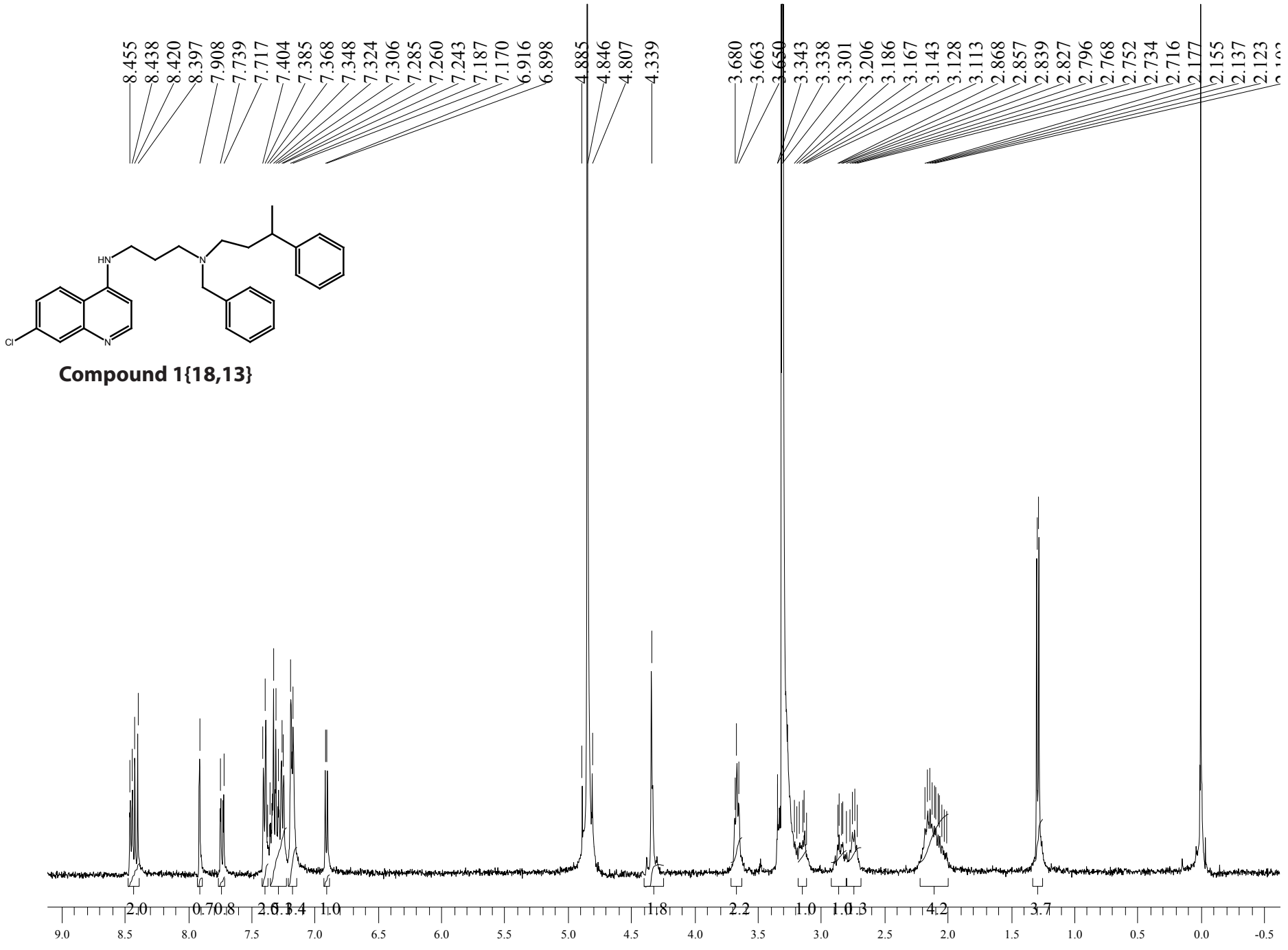


Compound 1{9,13}

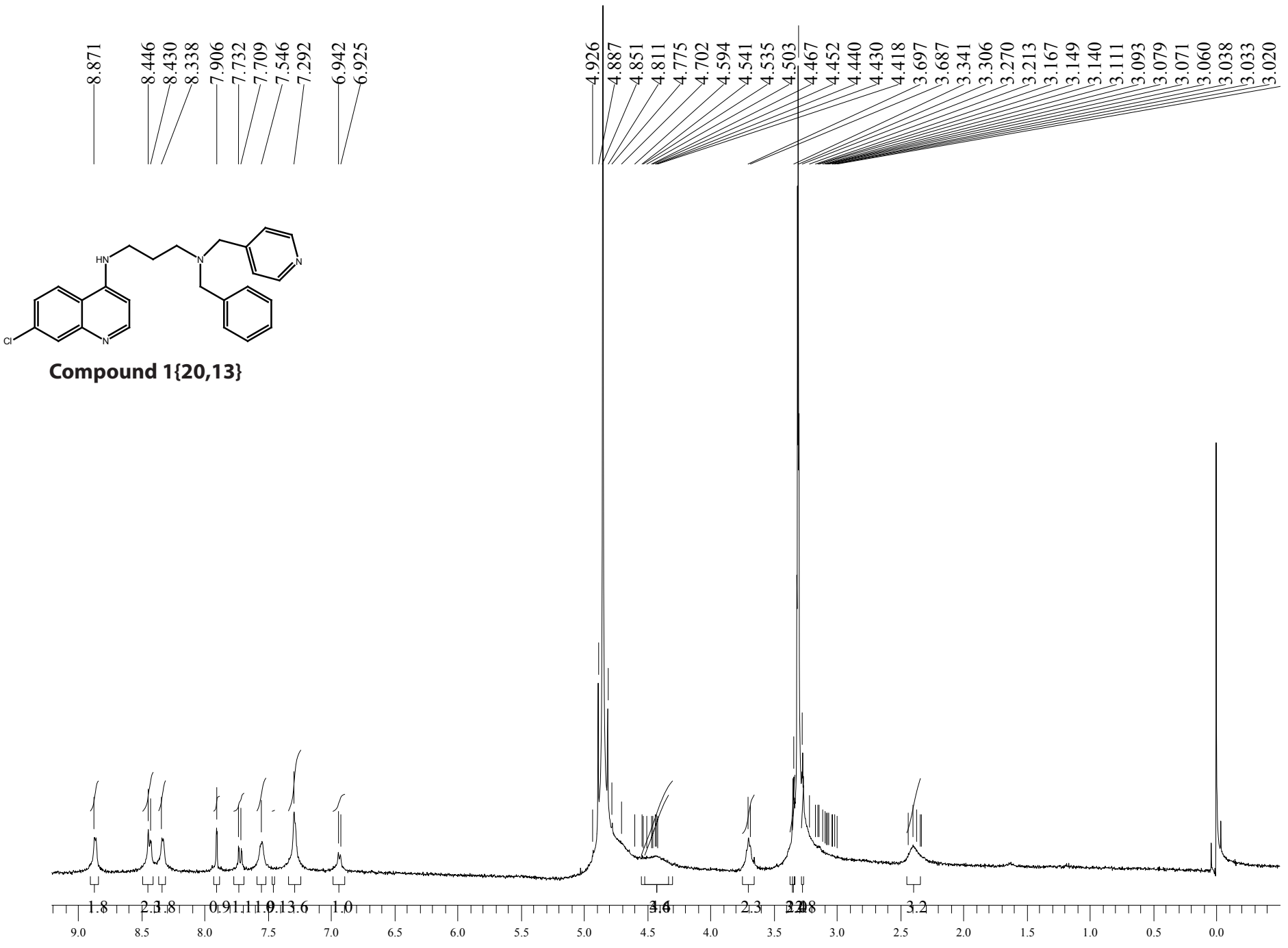

8.445
8.428
8.372
8.347
7.915
7.727
7.710
7.519
7.373
6.884
6.866
4.887
4.848
4.812
4.459
4.423
4.388
3.661
3.645
3.629
3.342
3.306
3.267
3.257
3.228
2.279
2.267
HN
N
Cl
N
Compound 1{13,13}
1.1
1.1
1.0
1.0
1.0
4.7
6.8
1.0
3.9
2.0
2.5
2.2
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5



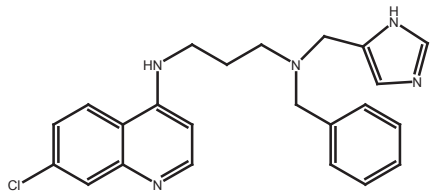
Compound 1{14,13}



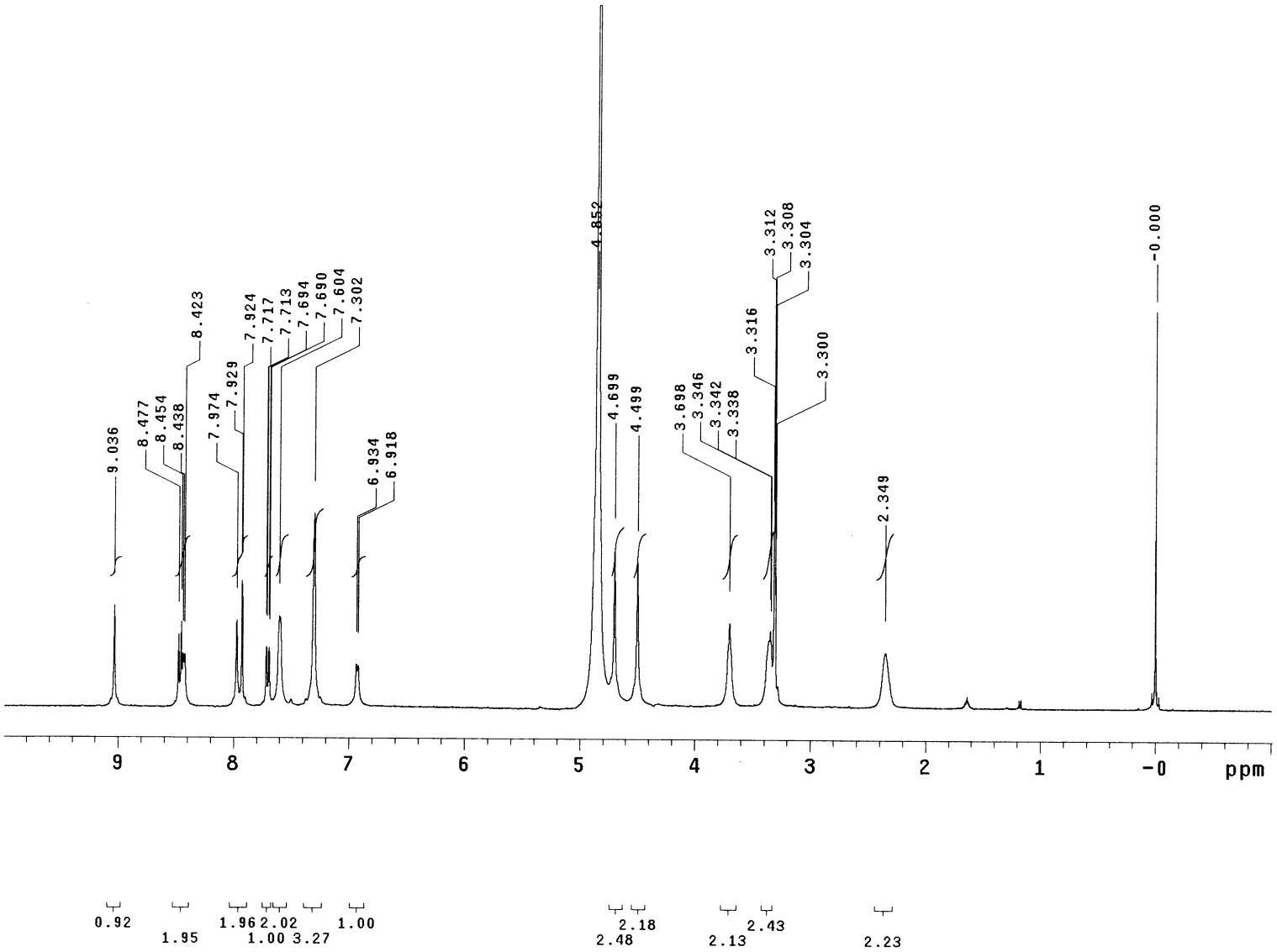
Compound 1{18,13}

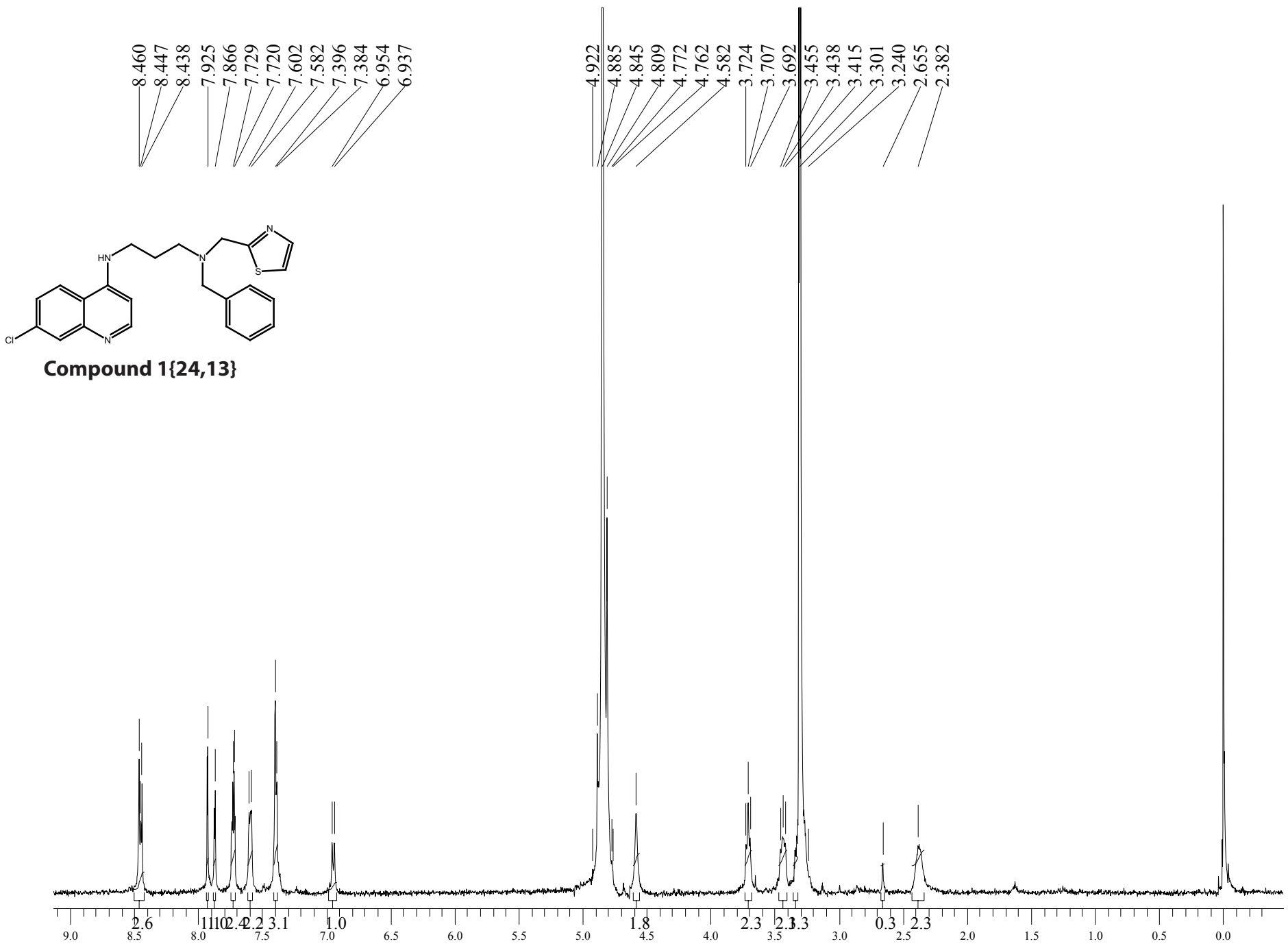


Compound 1{20,13}



Compound 1{23,13}





Compound 1{24,13}